THE NUTRITIONAL APPROACH TO EXPERIMENTAL DERMATOLOGY*

Introduction and Review of the Literature

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For many years the histopathologic changes in the majority of the dermatoses have been known and studied exhaustively. In no other branch of medicine has the anatomic and descriptive field received more attention. The student of skin diseases has at his disposal a wealth of carefully recorded and frequently confirmed data of the minute alterations of abnormal skin. Dermatologists often have sought means of utilizing this vast amount of histopathologic information by applying it experimentally, and have attempted to reproduce in animals skin diseases analogous to those of man.

If it were possible to secure a normal hairless beast whose skin was exactly comparable to the skin of man, the problems of comparative dermatology would be less difficult. Several species have been used experimentally but no animal has been found which has skin exactly comparable to human skin. The fur of beasts complicates the study of early skin changes by obscuring such signs as erythema. Although the histologic appearance of the skin of many animals bears a striking resemblance to the appearance of the skin of humans, there are differences in the skin appendages of various species. In health the care of the skin of the beast differs from that of man. The beast licks its healthy skin and escapes the detergent and drying action of soaps and excessive bathing unless it has been domesticated. In disease

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the beast excoriates by biting, licking and scratching in an effort to abate the discomforts of pruritus. However its nature spares it the almost invariable practice of man to apply or to have applied to his skin occlusives which prevent drainage, and irritants which cause superimposed dermatitis. The type of tissue response in different species is subject to variations and may lead to erroneous conclusions in comparative studies. Effects of temperature changes are not as marked in beasts as in man.

The most notable experimental dermatologic studies in animals have been those in which infections, particularly fungous infections, have been produced (1). In these experiments, diseases of already determined causes were reproduced. Because of the failure to ascertain infectious causes for many of the dermatoses, etiologic factors of disturbed metabolism and/or abnormal nutrition have always received attention and investigation.

A nutritional approach to experimental dermatology should begin with a thorough study in experimental animals of the skin diseases which can be produced by nutritional means. With the development of the science of nutrition there have appeared numerous contributions on the changes in the skins of various animals fed deficient or abnormal diets. Premature and erroneous interpretations of some of these findings have detracted from their importance, but a thorough appreciation of the work that has been done and of the mistakes that have been made should indicate to dermatologists that in the nutritional experimental approach there is a vast field. Although few complete analogues can be hoped for, the variety of skin lesions which have already been produced provide much biologic material for gross and histologic study.

For many reasons the rat is the ideal subject for nutritional experiments. Ease of breeding and low cost provide abundant biologic material. The short life cycle permits relatively brief experiments. With the rapid development of the science of nutrition studies with rats have been so extensive that more is known about the dietary requirements of this species than any other. In many respects the skin of the rat is similar to that of man. Rat skin differs mainly in that coil glands are rudimentary and the

epidermis is composed of fewer cell layers. It is possible to make certain gross and microscopic observations of rat's skin which reveal changes in the stratum corneum, the epidermis, the sebaceous glands, the connective tissue, the blood and lymph vessels and the cellular infiltrates. Whereas the thick fur of the rat may obscure certain early changes such as mild erythema or scaling, it should not deter the careful investigator who examines the skin of the rat with a technic similar to that employed by the dermatologist for the examination of a hair covered scalp.

Among the numerous nutritional investigations which have been reported in recent years there may be found many descriptions of skin changes which occur in amimals fed experimental diets. Localized and generalized alopecia, "denuding," alterations in the texture and the color of the hair, erythema, edema, scaling, dermatitis, ulceration, crust formation, purpura and atrophy have been reported to be associated with other signs of malnutrition. In many cases skin changes may be indications of the general poor condition of an animal which has been subjected to an abnormal diet. Such skin changes may represent a nonspecific symptom of deficiency, similar, for instance, to poor gain in weight. However we have found that certain deficiency states in animals are constantly accompanied by definite skin abnormalities and the assumption seems warranted that specific nutritional factors are essential for normal skin metabolism.

The intensive studies of the vitamin deficiencies have revealed various skin manifestations. Skin and mucous membrane changes have been remarked in rats which were fed diets deficient in vitamin A (2). The lesions appear when the animals are older than four months of age and are in the form of scabby ears and tails, sores on the nose, sore feet and ragged hair.

Lack of the B complex of vitamins other than thiamin has been particularly associated with dermatitis in several species and the symptoms in the diseases due to deficiency of this important group frequently have been described. These studies have demonstrated the multiple nature of this heat stable, water soluble fraction. The early work of Goldberger and Lillie (3), Sherman and Sandals (4) and many others, with deficiency of this complex showed that the heat stable fraction of the B complex was often associated with the production of a variety of skin changes. These changes were not always constant because only very crude vitamin preparations were then available. The isolation and synthesis of riboflavin provided the first means of differentiating in the rat the characteristic skin symptoms due to riboflavin deficiency and vitamin B_6 deficiency (5). Elve-

hjem and his associates showed that deficiency of nicotinic acid caused black tongue in dogs (6). Chick (7) showed that in pigs deprived of nicotinic acid a generalized eczematous dermatitis developed. It has been reported that pantothenic acid deficiency produces in chicks the typical dermatitis previously attributed to absence of the "filtrate factor" (8). Deficiency of other constituents of the filtrate fraction prepared from yeast, liver and other foods rich in this factor will cause greying of hair and follicular degeneration in the skin of rats, guinea pigs and puppies (9).

Since Holst and Frolich (10) demonstrated that scurvy could be produced in guinea pigs by feeding a diet of oats and bran, many investigators have produced hemorrhagic lesions by depleting this animal of vitamin C. A hemorrhagic disease of chicks due to vitamin K deficiency has been described (11).

The terminal stages of vitamin E deficiency in which there is a paralysis of the hind extremities, is frequently accompanied by an alopecia and scaling (12). The same condition will appear in the young of partially depleted females (13).

Changes in the integument have been associated with mineral deficiencies. Kruse, Orent and McCollum (14) have shown than magnesium deficiency in rats causes alopecia and dermatitis if the animals survive the early acute nervous phase of the disease. An interesting gingival hypertrophy also develops in these animals. Keil and Nelson (15) found that when rats were restricted to a milk diet the hair underwent marked changes in pigmentation; black hair became a silvery grey. They presented evidence that this change is dependent upon deficiency of copper. Hove, Elvehjem and Hart (16) produced a zinc deficiency in rats and observed interference with the development of hair. Sheep and cattle whose diets lack cobalt suffer from a microcytic hypochromic anemia and the skin is also affected (17). Deficiency of iodine causes hairlessness in the pig. The skin becomes "thickened, pulpy and very tender" (18).

There have been numerous studies of the rôle of proteins and amino acids in nutrition. Attention has been called to the effects of deficiency of certain amino acids upon the growth of hair and skin. Bosman (19) claims that underfeeding sheep so that they are deprived of sulphur containing amino acids reduces the weight of scoured fleece by 31.8 per cent and the fiber diameter by 36 per cent. Rats of Smuts, Mitchell and Hamilton (20) which received cystine deficient diets showed retardation of hair growth. Other workers have reported on the rôle of cystine in hair growth (21). Depletion of tryptophane causes loss of weight, loss of hair, hardening of the skin and depletion of fat stores in dogs (22). We have observed that patches of asymmetric as well as symmetric alopecia occur in animals which have been fed proteins of low biologic value.

The fat deficiency syndrome reported by Burr and Burr (23) is accompanied by changes in the skin which are prevented by the presence of unsaturated fatty acids in the diet. The most frequent symptoms are scaliness and necrosis of the tail.

Loss of hair may sometimes be a nonspecific or secondary symptom. Frequently we have observed patches of alopecia in numerous deficiency groups of the McCollum rat colony. In a miscellany of dietary experiments being conducted at any one time it is usually possible to find groups of rats showing alopecia. Often these alopecias are transient in duration. As a rule they are asymmetric and localized, but symmetric and generalized types also occur.

Although occasionally the mechanism of hair loss is by trichorrhexis, namely, breaking off of hairs by friction against other rats or against the cages, and/or trichotillomania, biting and pulling out of hairs, many times the shedding of hair is apparently spontaneous.

Other skin lesions have been experimentally produced by abnormal diets which contain an excess of one or more dietary constituents. Otherwise normal diets containing a high percent of dried unheated egg white produce a dermatitis which is curable by a factor contained in various natural foodstuffs, notably liver, brain, kidney and Irish potato. This condition has been carefully studied by Boas (24), György (25) and Parsons (26). The differential diagnosis of this disease and the several diseases due to lack of one or more vitamins of the B complex is now apparent.

Somekawa (27) fed rats a diet containing 10 to 15 per cent of natural whale oil and observed among other changes a striking skin symptom. An oily substance was diffused out from the skin in such great abundance that the rats appeared as though they had been dipped in oil.

Another interesting experimental dermatosis which has been produced in part by nutritional means is xanthoma. Anitschkow (28) fed rabbits diets containing large amounts of lecithin and typical tumors developed at sites in the skin which he had previously traumatized. By a similar technic Weidman (29) was able to obtain these lesions in dogs. Schaaf (30) fed rabbits anhydrous lanolin and produced xanthoma.

The majority of recorded observations of skin changes produced by nutritional means have been made by investigators other than physicians. It is not surprising that misinterpretations or even mistakes were made by some investigators, particularly biochemists, whose interest in skin changes was secondary to a desire for securing information concerning a chemical substance through biological procedure. At present there is a plethora of names of experimental skin diseases of nutritional origin. These are usually descriptive terms and are at times doubly unsatisfactory because they are imitative of descriptive terms of clinical dermatology. For example, the disease in rats due to a deficiency of vitamin B_6 has been called rat pellagra and rat acrodynia because of certain objective resemblances to the skin changes in these two human diseases (31). Visual inspection of B_6 deficient rats during certain stages gives the impression of morphologic similarities which are more apparent then real. Careful gross and microscopic examinations clearly disclose the dissimilarity of the animal disease and the two human diseases it is said to resemble. In the literature dealing with nutritional investigations there is often

confusion in the use of the following terms: dermatitis, scaling, alopecia, "denuding," pigmentation, crusting, excoriations, ulceration and fissuring. The term dermatitis has been abused by workers in the nutritional field with as much innocent consistency as the early dermatologist permitted the term eczema to suffer. It has been loosely applied to changes of the skin ranging from scaling to gangrene. Another example is the use of the term alopecia or loss of hair. Synonymously with the term alopecia, the term denuding is frequently found in the literature dealing with nutritional diseases. In our opinion this connotation is inexact and should be discouraged. Unless "denuded" is qualified by the word hair, it implies that the integument has been lost, as for example, in an ulcer. Crusting has often been used synonymously with scaling. Brownish crusts frequently have been mistaken for pigment. At times cyanosis has been confused with pigmentation.

We believe that perhaps the careful study of the gross and microscopic alterations of the skin of rats subjected to abnormal diets will be productive of some facts that eventually may be utilized in the elucidation of the causes of certain dermatoses which in man are apparently partially or wholly nutritional or metabolic in nature. Pitfalls are commonplace in comparative experiments. However it cannot be denied that the knowledge of the nutritional causes of several human diseases is the result of biochemical and histopathologic studies of animal tissue. Under the supervision of Dr. E. V. McCollum we have availed ourselves of an unusual opportunity in his department to study a variety of skin changes which we have produced in rats by feeding experimental diets. Descriptions of, and comments on these skin changes will be presented in a series of publications.

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